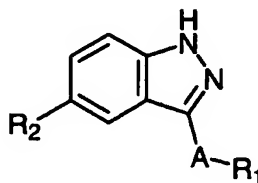


5 What is claimed is:

1. A method for treating, preventing and/or managing an asbestos-related disease or disorder in a patient, comprising administering to a patient in need thereof an effective amount of a JNK Inhibitor or a pharmaceutically acceptable salt thereof.

2. A method for treating, preventing and/or managing an asbestos-related disease or disorder in a patient, comprising administering to a patient in need thereof an effective amount of a compound having the following formula:



or a pharmaceutically acceptable salt thereof,

15 wherein:

A is a direct bond, $-(CH_2)_a-$, $-(CH_2)_bCH=CH(CH_2)_c-$, or $-(CH_2)_bC\equiv C(CH_2)_c-$;

R_1 is aryl, heteroaryl or heterocycle fused to phenyl, each being optionally substituted with one to four substituents independently selected from R_3 ;

R_2 is $-R_3$, $-R_4$, $-(CH_2)_bC(=O)R_5$, $-(CH_2)_bC(=O)OR_5$, $-(CH_2)_bC(=O)NR_5R_6$,
 20 $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$, $-(CH_2)_bNR_5C(=O)R_6$, $-(CH_2)_bNR_5C(=O)NR_6R_7$,
 $-(CH_2)_bNR_5R_6$, $-(CH_2)_bOR_5$, $-(CH_2)_bSO_dR_5$ or $-(CH_2)_bSO_2NR_5R_6$;

a is 1, 2, 3, 4, 5 or 6;

b and c are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4;

25 d is at each occurrence 0, 1 or 2;

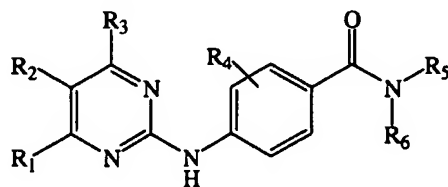
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- 5 R_3 is at each occurrence independently halogen, hydroxy, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, substituted aryl, arylalkyl, heterocycle, heterocycloalkyl, $-C(=O)OR_8$, $-OC(=O)R_8$, $-C(=O)NR_8R_9$, $-C(=O)NR_8OR_9$, $-SO_2NR_8R_9$, $-NR_8SO_2R_9$, $-CN$, $-NO_2$, $-NR_8R_9$, $-NR_8C(=O)R_9$, $-NR_8C(=O)(CH_2)_bOR_9$, $-NR_8C(=O)(CH_2)_bR_9$, $-O(CH_2)_bNR_8R_9$, or heterocycle fused to
 10 phenyl;

R_4 is alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, each being optionally substituted with one to four substituents independently selected from R_3 , or R_4 is halogen or hydroxy;

- 15 R_5 , R_6 and R_7 are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, wherein each of R_5 , R_6 and R_7 are optionally substituted with one to four substituents independently selected from R_3 ; and R_8 and R_9 are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle, or heterocycloalkyl, or R_8 and R_9 taken together with the atom or atoms to which they are bonded form a heterocycle, wherein each of R_8 , R_9 ,
 20 and R_8 and R_9 taken together to form a heterocycle are optionally substituted with one to four substituents independently selected from R_3 .

3. A method for treating, preventing and/or managing an asbestos-related disease or disorder in a patient, comprising administering to a patient in need thereof an effective
 25 amount of a compound having the following formula:



or a pharmaceutically acceptable salt thereof,

- 30 wherein:

- 5 R_1 is aryl or heteroaryl optionally substituted with one to four substituents independently selected from R_7 ;

R_2 is hydrogen;

R_3 is hydrogen or lower alkyl;

- 10 R_4 represents one to four optional substituents, wherein each substituent is the same or different and independently selected from halogen, hydroxy, lower alkyl and lower alkoxy;

- 15 R_5 and R_6 are the same or different and independently $-R_8$, $-(CH_2)_aC(=O)R_9$, $-(CH_2)_aC(=O)OR_9$, $-(CH_2)_aC(=O)NR_9R_{10}$, $-(CH_2)_aC(=O)NR_9(CH_2)_bC(=O)R_{10}$, $-(CH_2)_aNR_9C(=O)R_{10}$, $(CH_2)_aNR_{11}C(=O)NR_9R_{10}$, $-(CH_2)_aNR_9R_{10}$, $-(CH_2)_aOR_9$, $-(CH_2)_aSO_cR_9$ or $-(CH_2)_aSO_2NR_9R_{10}$;

or R_5 and R_6 taken together with the nitrogen atom to which they are attached to form a heterocycle or substituted heterocycle;

- 20 R_7 is at each occurrence independently halogen, hydroxy, cyano, nitro, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, $-C(=O)OR_8$, $-OC(=O)R_8$, $-C(=O)NR_8R_9$, $-C(=O)NR_8OR_9$, $-SO_cR_8$, $-SO_cNR_8R_9$, $-NR_8SO_cR_9$, $-NR_8R_9$, $-NR_8C(=O)R_9$, $-NR_8C(=O)(CH_2)_bOR_9$, $-NR_8C(=O)(CH_2)_bR_9$, $-O(CH_2)_bNR_8R_9$, or heterocycle fused to phenyl;

- 25 R_8 , R_9 , R_{10} and R_{11} are the same or different and at each occurrence independently hydrogen, alkyl, substituted alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl.;

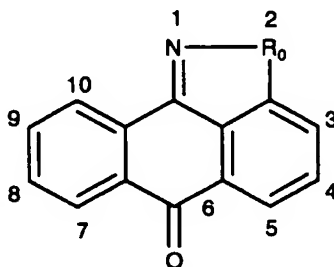
or R_8 and R_9 taken together with the atom or atoms to which they are attached to form a heterocycle;

a and b are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4; and

5 c is at each occurrence 0, 1 or 2.

4. A method for treating, preventing and/or managing an asbestos-related disease or disorder in a patient, comprising administering to a patient in need thereof an effective amount of a compound having the following formula:

10

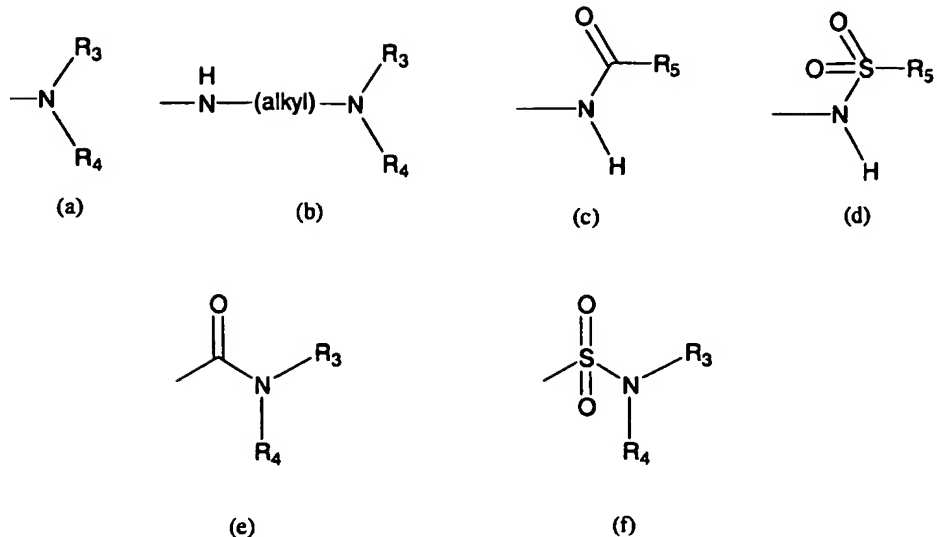


or a pharmaceutically acceptable salt thereof,

wherein R_0 is -O-, -S-, -S(O)-, -S(O)₂-, NH or -CH₂-;

the compound being (i) unsubstituted, (ii) monosubstituted and having a first substituent,
15 or (iii) disubstituted and having a first substituent and a second substituent;

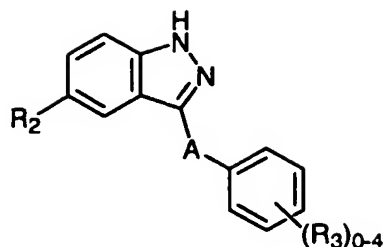
the first or second substituent, when present, is at the 3, 4, 5, 7, 8, 9, or 10 position,
wherein the first and second substituent, when present, are independently alkyl, hydroxy,
halogen, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy,
arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy,
20 aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, or a group represented by
formula (a), (b), (c), (d), (e), or (f):



- 5 wherein R_3 and R_4 are taken together and represent alkylidene or a heteroatom-containing cyclic alkylidene or R_3 and R_4 are independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl; and

- R_5 is hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, 10 alkoxyalkylalkyl, amino, mono-alkylamino, di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl, or di-alkylaminoalkyl.

5. The method of claim 2 wherein A is a direct bond.
6. The method of claim 2 wherein A is $\text{—(CH}_2\text{)}_a\text{—}$.
- 15 7. The method of claim 2 wherein A is $\text{—(CH}_2\text{)}_b\text{CH=CH(CH}_2\text{)}_c\text{—}$.
8. The method of claim 2 wherein A is $\text{—(CH}_2\text{)}_b\text{C}\equiv\text{C(CH}_2\text{)}_c\text{—}$.
9. The method of claim 2 wherein the compound has the following formula:



5

or a pharmaceutically acceptable salt thereof,

wherein:

A is a direct bond, $-(CH_2)_a-$, $-(CH_2)_bCH=CH(CH_2)_c-$, or $-(CH_2)_bC\equiv C(CH_2)_c-$;

10 R_1 is aryl, heteroaryl or heterocycle fused to phenyl, each being optionally substituted with one to four substituents independently selected from R_3 ;

R_2 is $-R_3$, $-R_4$, $-(CH_2)_bC(=O)R_5$, $-(CH_2)_bC(=O)OR_5$, $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$, $-(CH_2)_bNR_5C(=O)R_6$, $-(CH_2)_bNR_5C(=O)NR_6R_7$, $-(CH_2)_bNR_5R_6$, $-(CH_2)_bOR_5$, $-(CH_2)_bSO_dR_5$ or $-(CH_2)_bSO_2NR_5R_6$;

a is 1, 2, 3, 4, 5 or 6;

15 b and c are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4;

d is at each occurrence 0, 1 or 2;

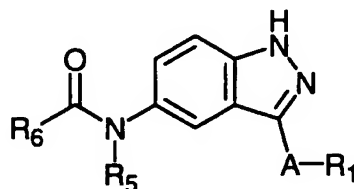
20 R_3 is at each occurrence independently halogen, hydroxy, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, $-C(=O)OR_8$, $-OC(=O)R_8$, $-C(=O)NR_8R_9$, $-C(=O)NR_8OR_9$, $-SO_2NR_8R_9$, $-NR_8SO_2R_9$, $-CN$, $-NO_2$, $-NR_8R_9$, $-NR_8C(=O)R_9$, $-NR_8C(=O)(CH_2)_bOR_9$, $-NR_8C(=O)(CH_2)_bR_9$, $-O(CH_2)_bNR_8R_9$, or heterocycle fused to phenyl;

25 R_4 is alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, each being optionally substituted with one to four substituents independently selected from R_3 , or R_4 is halogen or hydroxy;

- 5 R_5 , R_6 and R_7 are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, wherein each of R_5 , R_6 and R_7 are optionally substituted with one to four substituents independently selected from R_3 ; and
- R_8 and R_9 are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle, or heterocycloalkyl, or R_8 and R_9 taken together with
- 10 the atom or atoms to which they are bonded form a heterocycle, wherein each of R_8 , R_9 , and R_8 and R_9 taken together to form a heterocycle are optionally substituted with one to four substituents independently selected from R_3 .

10. The method of claim 2 wherein the compound has the following formula:

15



or a pharmaceutically acceptable salt thereof,

wherein:

- 20 A is a direct bond, $-(CH_2)_a-$, $-(CH_2)_bCH=CH(CH_2)_c-$, or $-(CH_2)_bC\equiv C(CH_2)_c-$;
- R_1 is aryl, heteroaryl or heterocycle fused to phenyl, each being optionally substituted with one to four substituents independently selected from R_3 ;
- R_2 is $-R_3$, $-R_4$, $-(CH_2)_bC(=O)R_5$, $-(CH_2)_bC(=O)OR_5$, $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$, $-(CH_2)_bNR_5C(=O)R_6$, $-(CH_2)_bNR_5C(=O)NR_6R_7$, $-(CH_2)_bNR_5R_6$, $-(CH_2)_bOR_5$, $-(CH_2)_bSO_2R_5$ or $-(CH_2)_bSO_2NR_5R_6$;
- 25 a is 1, 2, 3, 4, 5 or 6;
- b and c are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4;

5 *d* is at each occurrence 0, 1 or 2;

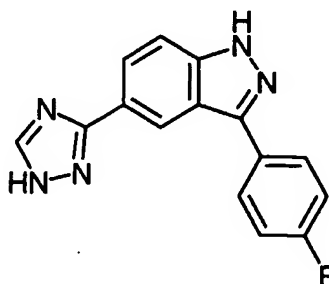
*R*₃ is at each occurrence independently halogen, hydroxy, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, -C(=O)OR₈, -OC(=O)R₈, -C(=O)NR₈R₉, -C(=O)NR₈OR₉, -SO₂NR₈R₉, -NR₈SO₂R₉, -CN, -NO₂, -NR₈R₉, -NR₈C(=O)R₉, -NR₈C(=O)(CH₂)_{*b*}OR₉, -
 10 NR₈C(=O)(CH₂)_{*b*}R₉, -O(CH₂)_{*b*}NR₈R₉, or heterocycle fused to phenyl;

*R*₄ is alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, each being optionally substituted with one to four substituents independently selected from *R*₃, or *R*₄ is halogen or hydroxy;

*R*₅, *R*₆ and *R*₇ are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, wherein each of *R*₅, *R*₆ and *R*₇ are
 15 optionally substituted with one to four substituents independently selected from *R*₃; and

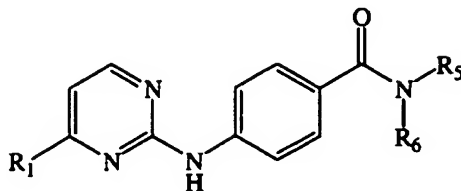
*R*₈ and *R*₉ are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle, or heterocycloalkyl, or *R*₈ and *R*₉ taken together with the atom or atoms to which they are bonded form a heterocycle, wherein each of *R*₈, *R*₉,
 20 and *R*₈ and *R*₉ taken together to form a heterocycle are optionally substituted with one to four substituents independently selected from *R*₃.

11. The method of claim 2 wherein the compound has the following formula:



25 or a pharmaceutically acceptable salt thereof.

- 5 12. The method of claim 3, wherein the compound has the following formula:



or a pharmaceutically acceptable salt thereof,

wherein:

- 10 R₁ is aryl or heteroaryl optionally substituted with one to four substituents independently selected from R₇;

R₂ is hydrogen;

R₃ is hydrogen or lower alkyl;

- 15 R₄ represents one to four optional substituents, wherein each substituent is the same or different and independently selected from halogen, hydroxy, lower alkyl and lower alkoxy;

- R₅ and R₆ are the same or different and independently -R₈, -(CH₂)_aC(=O)R₉, -
 (CH₂)_aC(=O)OR₉, -(CH₂)_aC(=O)NR₉R₁₀, -(CH₂)_aC(=O)NR₉(CH₂)_bC(=O)R₁₀, -
 (CH₂)_aNR₉C(=O)R₁₀, (CH₂)_aNR₁₁C(=O)NR₉R₁₀, -(CH₂)_aNR₉R₁₀, -(CH₂)_aOR₉, -
 20 (CH₂)_aSO_cR₉ or -(CH₂)_aSO₂NR₉R₁₀;

or R₅ and R₆ taken together with the nitrogen atom to which they are attached to form a heterocycle or substituted heterocycle;

- R₇ is at each occurrence independently halogen, hydroxy, cyano, nitro, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl,
 25 arylalkyl, heterocycle, heterocycloalkyl, -C(=O)OR₈, -OC(=O)R₈, -C(=O)NR₈R₉, -
 C(=O)NR₈OR₉, -SO_cR₈, -SO_cNR₈R₉, -NR₈SO_cR₉, -NR₈R₉, -NR₈C(=O)R₉, -

- 5 $\text{NR}_8\text{C}(=\text{O})(\text{CH}_2)_b\text{OR}_9$, $-\text{NR}_8\text{C}(=\text{O})(\text{CH}_2)_b\text{R}_9$, $-\text{O}(\text{CH}_2)_b\text{NR}_8\text{R}_9$, or heterocycle fused to phenyl;

R_8 , R_9 , R_{10} and R_{11} are the same or different and at each occurrence independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, arylalkyl, heterocycle, heterocycloalkyl;

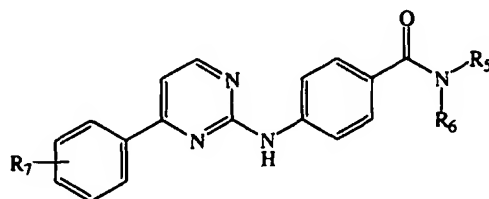
- 10 or R_8 and R_9 taken together with the atom or atoms to which they are attached to form a heterocycle;

a and b are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4; and

c is at each occurrence 0, 1 or 2.

15

13. The method of claim 3, wherein the compound has the following formula:



- 20 or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is aryl or heteroaryl optionally substituted with one to four substituents independently selected from R_7 ;

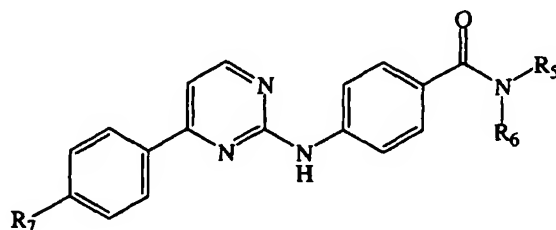
R_2 is hydrogen;

- 25 R_3 is hydrogen or lower alkyl;

R_4 represents one to four optional substituents, wherein each substituent is the same or different and independently selected from halogen, hydroxy, lower alkyl and lower alkoxy;

- 5 R_5 and R_6 are the same or different and independently $-R_8$, $-(CH_2)_aC(=O)R_9$, $-(CH_2)_aC(=O)OR_9$, $-(CH_2)_aC(=O)NR_9R_{10}$, $-(CH_2)_aC(=O)NR_9(CH_2)_bC(=O)R_{10}$, $-(CH_2)_aNR_9C(=O)R_{10}$, $(CH_2)_aNR_{11}C(=O)NR_9R_{10}$, $-(CH_2)_aNR_9R_{10}$, $-(CH_2)_aOR_9$, $-(CH_2)_aSO_2R_9$ or $-(CH_2)_aSO_2NR_9R_{10}$;
- or R_5 and R_6 taken together with the nitrogen atom to which they are attached to form a
- 10 heterocycle or substituted heterocycle;
- R_7 is at each occurrence independently halogen, hydroxy, cyano, nitro, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, $-C(=O)OR_8$, $-OC(=O)R_8$, $-C(=O)NR_8R_9$, $-C(=O)NR_8OR_9$, $-SO_2R_8$, $-SO_2NR_8R_9$, $-NR_8SO_2R_9$, $-NR_8R_9$, $-NR_8C(=O)R_9$, $-NR_8C(=O)(CH_2)_bOR_9$, $-NR_8C(=O)(CH_2)_bR_9$, $-O(CH_2)_bNR_8R_9$, or heterocycle fused to phenyl;
- 15 R_8 , R_9 , R_{10} and R_{11} are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl;
- or R_8 and R_9 taken together with the atom or atoms to which they are attached to form a
- 20 heterocycle;
- a and b are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4; and
- c is at each occurrence 0, 1 or 2.

- 25 14. The method of claim 3, wherein the compound has the following formula:



or a pharmaceutically acceptable salt thereof,

5 wherein:

R_1 is aryl or heteroaryl optionally substituted with one to four substituents independently selected from R_7 ;

R_2 is hydrogen;

R_3 is hydrogen or lower alkyl;

10 R_4 represents one to four optional substituents, wherein each substituent is the same or different and independently selected from halogen, hydroxy, lower alkyl and lower alkoxy;

R_5 and R_6 are the same or different and independently $-R_8$, $-(CH_2)_aC(=O)R_9$, $-(CH_2)_aC(=O)OR_9$, $-(CH_2)_aC(=O)NR_9R_{10}$, $-(CH_2)_aC(=O)NR_9(CH_2)_bC(=O)R_{10}$, $-(CH_2)_aNR_9C(=O)R_{10}$, $(CH_2)_aNR_{11}C(=O)NR_9R_{10}$, $-(CH_2)_aNR_9R_{10}$, $-(CH_2)_aOR_9$, $-(CH_2)_aSO_2R_9$ or $-(CH_2)_aSO_2NR_9R_{10}$;

15

or R_5 and R_6 taken together with the nitrogen atom to which they are attached to form a heterocycle;

R_7 is at each occurrence independently halogen, hydroxy, cyano, nitro, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, $-C(=O)OR_8$, $-OC(=O)R_8$, $-C(=O)NR_8R_9$, $-C(=O)NR_8OR_9$, $-SO_2R_8$, $-SO_2NR_8R_9$, $-NR_8SO_2R_9$, $-NR_8R_9$, $-NR_8C(=O)R_9$, $-NR_8C(=O)(CH_2)_bOR_9$, $-NR_8C(=O)(CH_2)_bR_9$, $-O(CH_2)_bNR_8R_9$, or heterocycle fused to phenyl;

20

25 R_8 , R_9 , R_{10} and R_{11} are the same or different and at each occurrence independently hydrogen, alkyl, substituted alkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl;

or R_8 and R_9 taken together with the atom or atoms to which they are attached to form a heterocycle;

5 *a* and *b* are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4; and

c is at each occurrence 0, 1 or 2.

10 15. The method of claim 4, wherein R_0 is -O-.

16. The method of claim 4, wherein R_0 is -S-.

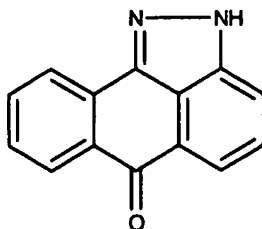
17. The method of claim 4, wherein R_0 is -S(O)-.

15 18. The method of claim 4, wherein R_0 is -S(O)₂-.

19. The method of claim 4, wherein R_0 is NH.

20 20. The method of claim 4, wherein R_0 is CH₂-.

21. The method of claim 4, wherein the compound has the following formula:



25 or a pharmaceutically acceptable salt thereof.

22. The method of claim 1, further comprising administering a second active agent.

23. The method of claim 2, further comprising administering a second active agent.

24. The method of claim 3, further comprising administering a second active agent.

- 5 25. The method of claim 4, further comprising administering a second active agent.
26. The method of claim 22, wherein the second active agent is an anti-cancer agent, antibiotic, anti-inflammatory agent, steroid, immunomodulatory agent, cytokine, immunosuppressive agent, an IMiD[®], a SelCID[®] or a combination thereof.
27. The method of claim 23, wherein the second active agent is anthracycline,
10 platinum, alkylating agent, interferon, oblimersen, cisplatin, cyclophosphamide, irinotecan, topotecan, temozolomide, temodar, carboplatin, procarbazine, gliadel, tamoxifen, methotrexate, taxotere, capecitabine, cisplatin, thiotepa, fludarabine, liposomal daunorubicin, cytarabine, doxetaxol, paclitaxel, vinblastine, GM-CSF, IL-2, dacarbazine, vinorelbine, zoledronic acid, palmitronate, biaxin, busulphan, prednisone,
15 bisphosphonate, arsenic trioxide, vincristine, doxorubicin, paclitaxel, ganciclovir, adriamycin, bleomycin, hyaluronidase, mitomycin C, mepacrine, thiotepa, tetracycline, thalidomide or gemcitabine.
28. The method of claim 1, wherein the disease or disorder is mesothelioma, asbestosis, pleural effusion, pleural plaque, pleural calcification, diffuse pleural
20 thickening, round atelectasis, or bronchogenic carcinoma.
29. A method of treating, preventing or managing an asbestos-related disease or disorder, which comprises administering to a patient in need of such treatment, prevention or management an effective amount of a JNK Inhibitor, or a pharmaceutically acceptable salt thereof, before, during or after chemotherapy, photodynamic therapy,
25 surgery, radiation therapy, gene therapy, or immunotherapy.

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